ment with little accumulated experience with how it will work or even if it can be made to work. Physicians have been assigned a peripheral rather than a central role. But if this is indeed to be the wave of the future for health care in this nation, physicians had best prepare to adapt; that is, find ways how to participate effectively in the deliberations of the HSA's at the various levels. This will be a new dimension of medical practice which will require new approaches and new applications of what may be old skills. Since in a very real sense the HSA's will have health care problems, the aim will be for local physicians to participate in these democratic processes, especially at the local level, in much the same way they guide, teach, advise and help any of their patients who have health care problems. And, as is so often the case in other forms of medical practice, this will often be wearing, time consuming and frustrating. But it is essential that knowledgeable practicing physicians become involved in these matters of health and health care. Those who do this and do it successfully will often be rendering service to their profession and to the public well above and beyond the traditional call of duty. In retrospect they may even prove to have been the medical heroes of this moment in the evolution of health care in this nation.

—MSMW

Diagnosing Megaloblastic Anemias

IN THIS ISSUE Carmel reviews the laboratory diagnosis of megaloblastic anemias, emphasizing well-established, reasonably accessible laboratory tests. Another excellent review of the diagnostic approach to megaloblastic anemia is that of Chanarin,[1] published in an issue of *Clinical Haematology* devoted entirely to the megaloblastic anemias. Like Chanarin, Carmel stresses the importance of an elevated mean corpuscular volume (MCV) (that is, macrocytosis) in "tipping off" the diagnosis of megaloblastosis. An important fact which should also be mentioned is that the megaloblastic red cell is not only large but also oval; that is, it is a macroovalocyte. Its oval character distinguishes it from those large red cells that occur in hypothyroidism, in aplastic anemia, in liver disease not associated with vitamin deficiency and in various hemolytic anemias.[2]

Carmel notes that the question is unsettled as to whether subtle vitamin deficiency may explain the neutrophil hypersegmentation which has been reported in iron deficiency. We believe this question may have finally been laid to rest by our recent findings[3,4] that almost invariably there is underlying folic acid deficiency in iron deficient patients with neutrophil hypersegmentation.

A particularly interesting very recent finding is the report by Clarkson and Mockridge at the American Society of Hematology Annual Meeting in San Diego in December 1977[5] that one of the earliest events in the development of folate deficiency is a reticulocytopenia and a macroreticulocytosis which is present before the mature red cells become large, and which is accompanied by a low serum folate level, but occurs before the mean red cell folate becomes low.

Carmel notes that the white cell changes in so-called erythroleukemia, more accurately described as DiGuglielmo syndrome or preleukemia, tend to be less classical. Actually, it is a striking fact that in this syndrome there may tend to be hyposegmentation rather than hypersegmentation.[2] This seems to be analagous to the pseudo-Pelger-Huet anomoly which occurs in about 10 percent of patients with myelogenous leukemia at one time or another during their clinical progression.

The Carmel review of serum and red cell folate indicates that much depends on how one chooses to define deficiency. Perhaps it would be clarifying to quote verbatim from conclusion number two of the Proceedings of the Workshop on Human Folate Requirements, published in 1977:[6]

> What constitutes appropriate assessment of nutritional status with regard to folate? Answer: Measurement of serum plus red cell folate appears to be the most practical approach. Current evidence suggests that, when serum and red cell folate are both low, other more direct indices of folate deficiency will be present (i.e., a low liver folate and a bone marrow "dU suppression" test demonstrating subnormal DNA synthesis by bone marrow cells correctable by adding folate or methylfolate *in vitro*). Measurement of tissue folate (i.e., red cell or liver folate) alone is not adequate because deficiency of vitamin B_{12} results in low tissue folate (but not low serum folate). Low serum folate alone is not adequate as a test for folate deficiency because it is too sensitive; i.e., serum folate is low after only three weeks of folate deprivation, which is months prior to exhaustion of tissue folate stores and development of biochemical folate deficiency.

As Carmel notes, in the first few days after folate therapy, red cell folate is still low and it still can be used to determine that folate deficiency was present. More recent studies indicate

that the lymphocyte dU suppression test may show the prior existence of folate or B_{12} deficiency as much as two months after vitamin therapy has been instituted.[7]

One can create in one's own laboratory, or purchase commercially, a kit capable of doing radioassay for both vitamin B_{12} and folic acid simultaneously, for roughly the cost and time of doing just one assay.[8]

One is inclined to agree with Carmel that the therapeutic trial is occasionally still of clinical utility. When it is done, the dose of folic acid should be 100 μg per day, and, when it is done with vitamin B_{12}, the dose should be 1 μg per day.[2]

Now that it is becoming clear that iron deficiency is present in a third to a half of all patients with megaloblastic anemia,[2] there are those who say that the old "shotgun therapy" approach was right all along. Not so. There was never anything wrong with "shotgun therapy," provided that one first made the correct diagnosis or diagnoses by appropriate testing. Such remains true today. If one draws blood for serum and red cell folate levels, serum vitamin B_{12} level, and does appropriate diagnostic tests for iron deficiency, then there is probably not much wrong with at that time starting "shotgun therapy" if one really wishes to. One can then be guided by the laboratory results as to what the deficiencies really are, and how the patient should properly be treated. "Shotgun therapy" without diagnostic evaluation first is as deplorable today as it was 40 years ago. Of course, if "shotgun therapy" is used, it may or may not be possible to diagnose a covert nutritional deficiency that is less severe than the most dominant deficiency.

Detection of malabsorption of vitamin B_{12} due to gastric or intestinal dysfunction[9] should include recognition of the important finding by Doscherholmen and Swaim[10] that the absorption of crystalline radioactive vitamin B_{12} may be normal in elderly people who subnormally absorb vitamin B_{12} from their food due to their hypochlorhydria or achlorhydria.

To the many possible causes of folate deficiency discussed by Carmel and by others,[2] must be added congenital defective transport of folate across cell walls.[11]

To the Carmel suggestion that reevaluation should be done in patients after therapy one can only say, "Amen," and add that one month after the start of vitamin therapy, reevaluation should be carried out in every patient with megaloblastic anemia for hidden iron deficiency which may only be measurable after the vitamin deficiency has been treated.[2]

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A Study of Potentially Compensable Events

ONE OF THE worthwhile results of the recent malpractice crisis in California was the decision of the California Medical Association and the California Hospital Association to sponsor the Medical Insurance Feasibility Study which is reported elsewhere in this issue. This objective study of 20,864 hospital charts from 23 representative hospitals in California developed a significant new method for measuring the frequency, causes and potential tort liability of adverse outcomes to patients in the course of health care management. The new measurement techniques which were created not only provide the most accurate information so far available, they also will be of great value in future applications.

The data are impressive. They are at once a measure of the relative safety and success of modern scientific medicine in the hospital setting where the risks are often great, but at the same